DISCLOSURES
Consultant for: Compass Therapeutics (until 2020), Anixa, Leidos, Alloy Therapeutics, Radyus Research.
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Honoraria from: Compass Therapeutics (until 2020), Anixa, Leidos, Alloy Therapeutics.
IgA and IgG dominate Ab secretion by tumor-associated plasmablasts in most ovarian carcinomas

Plasma cell: CD45+CD3-CD20-CD38+CD138+
Plasmablast: CD45+CD3-CD19+CD20-CD38highCD27high
B cell: CD45+CD3-CD19+CD20+

Biswa et al; Nature; 2021
What are the specificities of antibodies produced by TLS$^+$ tumor-associated B cells?
Established bank of viable dissociated tumor cells

Separation of viable B cells from TLS+ tumors

CD40/IL-21 activation + EBV immortalization

Antibody purification from supernatants

Screening of reactivities using Proteome arrays

Sorting of reactive B cells using tetramerized biotinylated peptides

Cloning ovarian cancer-reactive B cells
Sorting of B cells reacting against extracellular domains using biotinylated peptides

Biotinylated Antigen + Fluorescent Streptavidin + Tetramer → B cell labelling → Sorting

Biswas et al; Nature; 2021
Expanded B cells reacting against extracellular domains using biotinylated peptides retain specificity
Tumor-derived IgA antibodies exert immune pressure against tumor growth
Tumor-derived IgA antibodies exert immune pressure against tumor growth through different mechanisms.

RAG1 mouse PBS vs IgG Combined

IgG does NOT accelerate tumor growth!!!
Why irrelevant IgA has anti-tumor activity in an Fc-dependent manner?
plgR binds polymeric IgA for transcytosis through epithelial cells and luminal secretion.
Most epithelial cancers express PIGR (TCGA)
IgA transcytoses inside plgR+ ovarian cancer cells (release of secretory component upon incubation with IgA)

OVCAR3 cells + IgA/IgG → Supernatant → Mass Spectrometry

Biswa et al; Nature; 2021
Tumor-derived IgA antibodies elicit protective immune responses through antigen-independent and antigen-dependent mechanisms.
What about other histological subtypes of ovarian cancer?
Endometriosis is a premalignant lesion for aggressive ovarian cancers

-1/10 women will develop endometriosis during their reproductive years

-10-fold increase in probability of developing clear cell ovarian cancer (5-10% of EOC in Western world; 25% in Asia)

-5-fold increase in probability of developing endometrioid ovarian cancer (8-15% of EOC)

-Increased probability of developing HGSOC (~70% of EOC)
Molecules with extracellular domains targeted by Abs derived from endometriosis and endometriosis-associated ovarian cancers

OLFML2B
- Amplified in ~5% of other gyn/onc malignancies
- Reported association with short survival in gastric cancer
- Co-expressed with ADAM family metallopeptidases, fibrillar collagen proteins and the fibroblast protein FAP → orchestration of stroma and the extracellular matrix.

SDCBP
- Elevated in a wide range of cancers, including melanoma and glioblastoma.
- Links syndecan-mediated signaling to the cytoskeleton → Metastatic driver.
- Drives autophagy to prevent anoikis.
- Promotes chemoresistance in colo-rectal cancer.

2 endometriomas (Ponce, PR), 2 stage III clear cell ovarian cancers, 2 stage III endometrioid ovarian cancers
Generating CAR T cells using scFv sequences from tumor-derived Abs
Generation of an OR5V1 CAR from BCR sequences clonally expanded at tumor beds

Chimeric antigen receptor against OR5V1:

Heavy chain peptide: VH; Spacer: C; IG hinge domain: C

Light chain peptide: 4-188 C domain; CDR4-6

Tumor-derived immortalized B cells

OR5V1-reactive B cell sorting

Droplet encapsulation

scBCR-seq
Targeting OR5V1 with CAR T cells that use a scFV derived from ovarian cancer Abs
Tumor-derived OR5V1 CAR T cells abrogate HeLa tumor growth in vivo

**In vivo experiment 2, n=5 NSG mice/group**
Generating CAR T cells against other olfactory receptors (OR2H1)
OR2H1 is expressed in multiple human tumors, but not most healthy tissues (with the exception of testis).

TCGA (7%-69% of carcinomas)

Healthy tissues (our own analysis)
OR2H1 is expressed in human ovarian cancer

HGSOC
(>25% positivity in TCGA)

NSCLC
(9-10% positivity in TCGA)

Breast cancer
(8% positivity in TCGA)

Other ovarian cancers
(all positive)
OR2H1 CAR T cells abrogate NSCLC growth in vivo
OR2H1 CAR T cells control OR2H1\textsuperscript{low} OVCAR3 (HGSOC) tumor growth
IND approval for FSHCER T cells targeting FSHR+ ovarian cancer (IND:27225)
FSH-targeted chimeric receptors re-direct primary human T cells against FSHR+ ovarian cancer cells

**IND# 27225:**

Autologous CD3+T cells transduced w/ gamma retroviral vector, pMSGV1, for FSHR-specific 4-1BB/CD3 chimeric endocrine receptor expression, Intraperitoneal (IP)/Intravenous (IV) infusion
FSH-re-directed autologous human T cells effectively target orthotopic patient-derived FSHR+ tumors in vivo (II)

10e7 AUTOLOGOUS CERT cells IP

IND# 27225:

Autologous CD3+T cells transduced w/ gamma retroviral vector, pMSGV1, for FSHR-specific 4-1BB/CD3 chimeric endocrine receptor expression, Intraperitoneal (IP)/Intravenous (IV) infusion
CONCLUSIONS

→ T and B cell responses act in coordination in HGSOC.

→ IgA elicits antigen-specific and non-antigen-specific (PIGR-dependent) anti-tumor effects in EOC.

→ Tumor-derived Abs targeting extracellular molecules abrogate ovarian cancer progression.

→ CAR T cells against ovarian cancer can be generated from BCR sequences clonally expanded at tumor beds.

→ OR2H1 CAR T cells can target a variety of human cancers.

→ FSH-targeted T cells expressing chimeric receptors kill established ovarian tumors.
Conejo-Garcia Lab (current members)
Carmen Anadon-Galindo
Ricardo Chaurio
Jessica Mine
Alexandra Martin (Gyn/Onc)
Kim Sprenger
Subir Biswas
Gunjan Mandal
Pat Innamarato
Carla Cortina
John Powers

Collaborators (Moffitt)
J. Pinilla
M. Davila
R. Wenham
S. Tworoger
D. Abate-Daga
B. Perez
R. Li
T. Robinson
X. Wang
X. Yu
P. Rodriguez

Collaborators (U. Buenos Aires)
G. Rabinovich

Collaborators (Cornell)
J. Cubillos-Ruiz

Collaborators (U Pittsburgh)
R. Buckanovich

Collaborators (U Texas: S. Antonio)
Tyler Curiel

Collaborators (Ponce, PR)
I. Flores

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Conejo-Garcia Lab (alumni involved in this work)
Andrea Buras (Gyn/Onc, Michigan)
Sumit Mehta (Gyn/Onc (Moffitt))
Kyle Payne (Rutgers)

Collaborators (Ponce, PR)
I. Flores

Collaborators (U. Buenos Aires)
G. Rabinovich

Collaborators (Cornell)
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